NTP
National Toxicology Program

Research Concept for Hydroquinone

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Nomination

- Hydroquinone (HQ) was nominated by the U.S. FDA for toxicological evaluation
- Rationale:
  - Data are needed to evaluate the risk of exposure to HQ in topically applied consumer products
- Specific studies requested:
  - Reproductive toxicity studies in animals
  - Dermal toxicity and carcinogenicity studies in animals
    - An animal model expressing melanocytes is needed to investigate toxicity in the skin

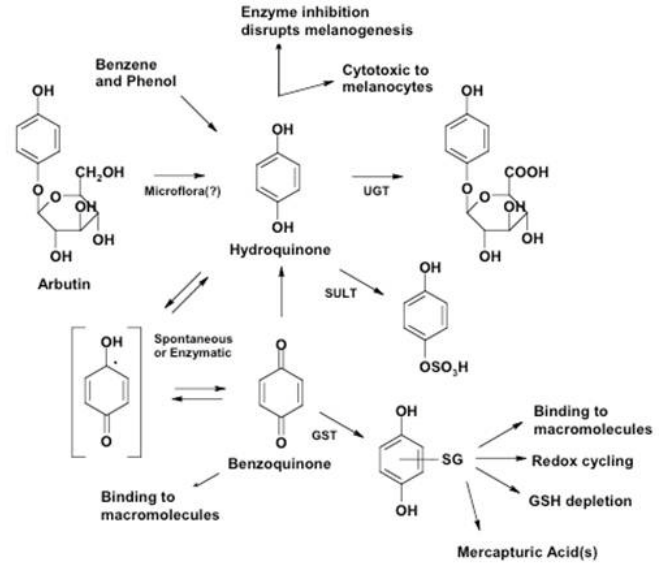
Background

- HQ and its glucose conjugate, arbutin, occur naturally (In coffee, tea, red wine, wheat, onions, pears, and bearberry extract)
- Synthesized (used as reducing agent, antioxidant, stabilizer, or inhibitor)
- Used in topical medicines to treat disorders of skin pigmentation and in over-the-counter (OTC) products for skin bleaching
  - HQ inhibits melanin production and damages melanocytes
- Toxicity
  - Evidence of clastogenicity
  - Neurotoxic at high doses (rodents and humans)
  - Evidence of reproductive toxicity in rodents
  - Evidence of carcinogenicity in rodents in 2-year oral bioassay
  - Dermal toxicity in humans using topical preparations containing HQ
    - Vitiligo: Loss of melanocytes
    - Ochronosis: Hyperpigmentation

Background: Previous NTP toxicity studies of HQ

- Dermal 14-day studies in F344/N rats and B6C3F1 mice (≤ 4800 mg/kg)
  - No clinical signs of toxicity
- Oral 14-day studies in rats and mice (≤ 1000 mg/kg)
  - Decreased body weights, tremors or convulsions, mortality
- Oral 90-day studies in rats and mice (≤ 400 mg/kg)
  - Mortality and CNS effects (rats/mice), nephrotoxicity (rats), and forestomach toxicity (mice) ≥ 200 mg/kg. Little toxicity at lower doses
- Oral 2-year studies in the rat and mouse (≤ 100 mg/kg)
  - Increased incidence of kidney adenomas in male rats, leukemia in female rats, and liver adenomas or carcinomas in female mice

Background: Mechanisms of action



Adapted from DeCaprio (1999)

Key Issues: Dermal exposure and toxicity

- The safety of topical OTC preparations containing HQ is in doubt
- No chronic toxicity data are available in animals following dermal exposure to HQ
- Effect of long-term dermal exposure on systemic toxicity is uncertain
  - Internal dose and formation of reactive metabolite(s)?
- Toxicity at the site of application is uncertain
  - Melanocyte damage and tumorigenicity in skin of pigmented animals?

Key Issues: HQ and reproductive toxicity

- The existing reproductive toxicity data in animal models are conflicting and incomplete
  - Increased fetal resorption and disrupted estrus cycle, spermatogenesis and fertility observed in some studies
  - Other studies were negative for reproductive effects
  - Inconsistencies may be due to methodology or studies that were not comprehensive

Proposed Research Program

- Goal: Provide toxicological data in NTP rodent models for use in evaluating the risk to humans following dermal exposure to HQ
- Specific aims:
  1. Conduct ADME studies
  2. Conduct reproductive toxicity studies
  3. Conduct dermal toxicity and carcinogenicity studies

Aim 1: Conduct ADME studies of HQ in rodents

- Oral studies in the Sprague-Dawley (SD) rat and B6C3F1 mouse
  - Provide interpretive data for oral reproductive toxicity studies
  - Provide comparative data for dermal ADME studies
- Dermal studies in the SD rat and B6C3F1 mouse
  - Determine the effect of the route of administration on the fate of HQ
    - Quantitate internal dose and metabolism
  - Needed for design and interpretation of dermal toxicity studies
- Conduct limited studies in the F344/N rat if needed
  - Provide comparative data for previous NTP toxicity studies

Aim 2: Conduct reproductive toxicity studies of HQ in rodents

- Conduct studies in rats using the NTP Reproductive Assessment by Continuous Breeding (RACB) protocol (oral route only)
  - Provide rigorous investigation of reproductive effects
  - Address fertility effects of HQ
- Add developmental toxicity studies if effects are observed in the RACB studies

Aim 3: Conduct dermal toxicity and carcinogenicity studies of HQ in rodents

- Conduct 90-day dermal studies in the SD rat and B6C3F1 mouse
  - Extend the previous NTP 14-day dermal studies to subchronic exposure
  - Endpoints: Clinical signs, histopathology, and observations for toxicity in the skin of the albino rat and pigmented mouse
  - Results will determine the design of 2-year studies
- Conduct 2-year chronic bioassays by the dermal route in the SD rat and the B6C3F1 mouse

Significance of Proposed Research Program

- Provides toxicological data needed by the U.S. FDA to evaluate the risk of exposure to HQ in topically applied consumer products

Acknowledgement

• Representatives of the U.S. FDA involved in the development of the concept and in future study design